EXHIBIT 14

Office Action Summary	Application No.	Applicant(s)	
	11/451,707	OLSON ET AL.	
	Examiner	Art Unit	
	Jeffrey S. Parkin	1648	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *03* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/14/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Applicants: Graham P. Allaway et al.
Serial No.: 09/888,938
Filed: June 25, 2001
Exhibit 14

Detailed Office Action

Status of the Claims

Acknowledgement is hereby made of receipt and entry of amendment filed 14 October, 2008. Claims 33-55 are pending in the instant application.

Information Disclosure Statement

The information disclosure statement filed 14 October, 2008, has been placed in the application file and the information referred to therein has been considered.

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claim 55 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

35 U.S.C. § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and

> exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Biological Deposit Requirement

Claims 33 and 34 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure for the claimed invention. As previously set forth, it is apparent that the monoclonal antibody PA14, as well as, the hybridoma cell line expressing it (ATCC Accession No. HB-12610), are required to practice the claimed invention. As required elements, they must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If they are not so obtainable or available, the enablement requirements of 35 U.S.C. § 112, first paragraph, may be satisfied by a deposit of the hybridoma cell line producing said antibody. See 37 C.F.R. § 1.802.

Due to the unpredictability associated with antibody production (i.e., each antibody generally has a unique structure) and the failure of the specification to provide any detailed structural information concerning the claimed antibodies, antibodies PA-14 and CD4-IgG2 do not appear to be readily available materials.[1] Deposit of the hybridoma cell lines producing said antibodies or detailed structural information (i.e., the complete nucleotide or amino acid sequence of each

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1 It has been well-documented that most animals are capable of producing a vast repertoire of structurally and functionally distinct antibodies. For instance, conservative estimates suggest that humans are capable of producing over 32 million different combinations of light and heavy chains. This estimate excludes various other sources of diversity. See "Immunoglobulins: Molecular Genetics", in *Fundamental Immunology, Fourth Edition*, W. E. Paul, ed., Lippincott-Raven Publishers, Philadelphia, 1999, pp. 142-143.

antibody) would satisfy the enablement requirements of 35 U.S.C. § 112. If a deposit is made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made under the terms of the Budapest Treaty **and** that **all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent, would satisfy the deposit requirements**. See 37 C.F.R. § .1.808.

If the deposits have not been made under the provisions of the Budapest Treaty, then an affidavit or declaration by Applicants or someone associated with the patent owner who is in a position to make such assurances, or a statement by an attorney of record over his or her signature, stating that the deposit has been made at an acceptable depository and that the following criteria have been met:

(a) during the pendency of the application, access to the deposits will be afforded to one determined by the Commissioner to be entitled thereto;

(b) all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent;

(c) the deposits will be maintained for a term of at least thirty (30) years and at least five (5) years after the most recent request for the furnishing of a sample of the deposited material;

(d) a viability statement in accordance with the provisions of 37 C.F.R. § .1.807; and

(e) the deposit will be replaced should it become necessary due to inviability, contamination or loss of capability to function in the manner described in the specification.

In addition, the identifying information set forth in 37 C.F.R. § 1.809(d) should be added to the specification. See 37 C.F.R. § 1.803-1.809 for additional explanation of these requirements. Perusal of the specification revealed that a hybridoma expressing PA14 and expression vectors encoding CD4-IgG2 have been deposited with the ATCC. However, applicants are reminded that a statement specifying that **all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent** must also be provided. Accordingly, the biological deposit requirements have not been fulfilled.

Response to Arguments

Applicants asserted that Exhibit A, which addressed all of the issues raised *supra*, was provided in the most recent response. Unfortunately, a copy of this exhibit was not present in the electronic file wrapper. Applicants are invited to provide another copy of the exhibit at their earliest convenience.

Scope of Enablement

Claims 33-55 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The claims are broadly directed toward methods of reducing the HIV-1 viral load in a

subject by administering a PA14 monoclonal antibody or an antibody that cross-competes with PA14 for binding to CCR5 (claim 33). Claim 55 is also directed toward a method of reducing the HIV-1 viral load in a subject by administering an IgG Mab with the recited properties (e.g., CCR5 binding; inhibits gp120/sCD4 complex binding to CCR5; inhibits HIV-1 fusion to CCR5+ cells; and recognizes an epitope in the N-terminus and second extracellular loop of CCR5. The specification discloses the identification and preliminary characterization of a small panel of six Mabs designated PA8, PA9, PA10, PA11, PA12, and PA14. PA14/PRO140 appears to display the greatest antiviral activity. As previously set forth, appropriately drafted claim language directed toward this embodiment would obviate the rejection.

The legal considerations that govern enablement determinations pertaining to undue experimentation have been clearly set forth. *Enzo Biochem, Inc.*, 52 U.S.P.Q.2d 1129 (C.A.F.C. 1999). *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988). *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows:

1) The claims encompass a potentially large genus of structurally/functionally distinct immunoglobulins. The claims simply specify that any antibody that cross-competes with PA14 for CCR5 binding can be employed. Thus, the claims encompass antibodies that recognize linear epitopes nearby or conformational epitopes encompassing several regions of CCR5. The claimed functional limitations are insufficient to support the full breadth of the claim language desired because they fail to provide any structural guidance (e.g., binding specificity, affinity, avidity, etc.) pertaining to the amino acid sequence of the Ab of interest.

2) The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating antigen-antibody binding interactions. Concerning claim 33, there is no discussion about those CCR5 epitopes that lead to the development of a high-titer neutralizing immune response. Although claim 55 includes a limitation suggesting the antibody of interest binds to an epitope comprising the N-terminus and second extracellular loop of CCR5, it fails to actually set forth the antigenic determinants required for antibody binding. Thus, the skilled artisan cannot determine if any given competing antibody will prove to be a useful therapeutic.

3) The disclosure fails to provide adequate guidance pertaining to the immunological properties of any given antibody. There is no discussion concerning the binding affinity, avidity, specificity, titer, etc. of any given antibody. Simply identifying antibodies that cross-compete with PA14 for CCR5 binding does not guarantee that said antibodies will have the requisite immunological properties that make them useful therapeutically.

4) The disclosure fails to provide a sufficient number of working embodiments. Considering the claim breadth, it would require more than a single Mab to enable the full breadth of the claimed invention.

5) The development of HIV immunotherapeutics has been problematic and ineffective (Montefiori, 2005; Haynes *et al.*, 2005; Trkola *et al.*, 2005). This is due to poor titers and binding affinities of the Mabs of interest. It has proven to be a difficult undertaking identifying therapeutically useful Mabs for the treatment of HIV-1 infection.

When all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention.

Response to Arguments

Applicants traverse and submit the claim limitations and specification provide sufficient structural/functional guidance to enable the full breadth of the patent protection desired. Applicants further note that the specification provides the epitope recognized by PA14. Finally, applicants submit that sufficient structural/functional language is provided thereby rendering further immunological characterization of the antibody unnecessary. These arguments are not deemed to be persuasive. First, although the specification provides a preliminary analysis of the region involved in antigen-antibody binding, it still fails to identify the molecular determinants required. The epitope in question appears to a conformational determinant. Thus, it will be difficult to ascertain which amino acids are critical for antigen-antibody binding interactions without further detailed mapping studies. Second, simply identifying an

a Mab that "cross-competes" with PA14 for binding, does not mean that said Mab will have the requisite properties to be a useful therapeutic. For instance, the Mab could easily bind to an adjacent non-neutralizing epitope and still inhibit PA14 binding. Third, with the exception of Mab PA14, the dearth of structural information is problematic. Simply providing a vague reference to the regions of CCR5 which encompass the epitope of interest does not lead the skilled artisan to the precise molecular determinants modulating antigen-antibody binding. Thus, the rejection is properly maintained.

35 U.S.C. § 103(a)

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The previous rejection of claims 33-55 under 35 U.S.C. § 103(a) as being unpatentable over Wu and Mackay (1998), is hereby withdrawn in response to applicants' amendment.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 U.S.P.Q.2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); and *In re Thorington*, 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969). A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(c) or § 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

Provisional Rejections

Claims 33-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 33-41 of copending Application No. 11/316,078. Although the conflicting claims are not identical,

they are not patentably distinct from each other. The claims of the '078 application are directed toward methods for reducing the viral load of HIV-1 by administering IgG Mabs that bind to CCR5. Accordingly, these claims are not patentably distinct from those in the instant application. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicants maintain that a terminal disclaimer will be filed, if appropriate, upon the identification of allowable subject matter.

Claims 33-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 52-70 of copending Application No. 11/520,556. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '556 application are directed toward HIV-1 inhibitory methods employing PA14 and are not patentably distinct from the claims of the instant invention. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicants maintain that a terminal disclaimer will be filed, if appropriate, upon the identification of allowable subject matter.

Claims 33-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 98-112 of copending Application No. 11/804,746. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of

the '746 application are directed toward HIV-1 inhibitory methods employing PA14 and are not patentably distinct from the claims of the instant invention. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicants maintain that a terminal disclaimer will be filed, if appropriate, upon the identification of allowable subject matter.

Claims 33-55 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 61 of copending Application No. 11/894,568. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '568 application are directed toward HIV-1 inhibitory methods employing CCR5-specific Mabs, some of which would be expected to display the same binding characteristics of PA14. Accordingly the inventions are not patentably distinct. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Applicants maintain that a terminal disclaimer will be filed, if appropriate, upon the identification of allowable subject matter.

Non-provisional rejections

Claims 33-55 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-24 of U.S. Patent No. 7,060,273. Although the conflicting claims are not identical, they are not patentably distinct from each other. The claims of the '273 patent are

directed toward methods of reducing the HIV-1 viral load in a subject by administering an anti-CCR5 Mab that comprises the CDRs from PA14. Thus, the claims encompass PA14 administration and are not patentably distinct from the instant invention. Applicants maintain that a terminal disclaimer will be filed, if appropriate, upon the identification of allowable subject matter.

Action Is Final

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a). A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Correspondence

Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (571) 272-0908. The examiner can normally be reached Monday through Thursday from 10:30 AM to 9:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Bruce R. Campell, Ph.D., can be reached at (571) 272-0974. Direct general status inquiries to the Technology Center 1600

receptionist at (571) 272-1600. Informal communications may be submitted to the Examiner's RightFAX account at (571) 273-0908.

Applicants are reminded that the United States Patent and Trademark Office (Office) requires most patent related correspondence to be: a) faxed to the Central FAX number (571-273-8300) (updated as of July 15, 2005), b) hand carried or delivered to the Customer Service Window (now located at the Randolph Building, 401 Dulany Street, Alexandria, VA 22314), c) mailed to the mailing address set forth in 37 C.F.R. § 1.1 (e.g., P.O. Box 1450, Alexandria, VA 22313-1450), or d) transmitted to the Office using the Office's Electronic Filing System. This notice replaces all prior Office notices specifying a specific fax number or hand carry address for certain patent related correspondence. For further information refer to the Updated Notice of Centralized Delivery and Facsimile Transmission Policy for Patent Related Correspondence, and Exceptions Thereto, 1292 Off. Gaz. Pat. Office 186 (March 29, 2005).

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully,

/Jeffrey S. Parkin/

Jeffrey S. Parkin, Ph.D.
Primary Examiner
Art Unit 1648

04 January, 2009

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11/451,707	06/12/2006	William C. Olson	64672-AB / JPW / AG	2878

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.